REMARKS

I. Amendments to the Claims

Currently, claims 4-8, 12-14, 16, and 37-58 are pending in the application with claims 4, 12, 16, 46, and 47 being the independent claims. Claims 9-11 and 18-36 were withdrawn, as being directed to a non-elected invention. Claims 4, 7, 12, 16, 46, and 47 have been amended, and new claims 54-58 have been added. Claims 15 and 17 and withdrawn claims 9-11 and 18-36 were previously canceled without prejudice to their pursuit in an appropriate continuation or divisional application.

Support for the amendments to claims 4, 7, 12, 16, 46, and 47 and for new claims 54-58 can be found throughout the specification and claims as originally filed, particularly on pages 8-16 and 18-27 and throughout the concurrently filed Preliminary Amendment, particularly in Example 7.

Additional support for the amendments to claims 4, 12, 16, 46, and 47 be found, e.g., on page 8, lines 3-22; from page 9, line 4, to page 12, line 14; from page 15, line 9, to page 16, line 6; and in the Examples. Additional support for the amendments to claims 4, 12, 16, 46, and 47 can be found, e.g., from page 8, line 3, to page 9, line 22; from page 10, line 16, to page 12, line 14; on page 14, lines 19-23; from page 15, line 9, to page 16, line 6; on page 19, lines 17-19; and in the Examples. Additional support for the amendments to claims 7, 12, 16, and 46, and for new claims 54-58 can be found, e.g., on page 6, line 29; on page 7, line 5; and from page 13, line 28, to page 14, line 9.

II. Status of the Claims

Claims 1-36 were previously in the application. Claims 4-8 and 12-17 were elected in response to the Restriction Requirement. Claims 9-11 and 18-36 were withdrawn as being directed to a non-elected invention.

In an earlier filed Amendment (January 22, 2007), claims 4-8, 12, and 16 were amended, and new claims 37-52 were added. Claims 15 and 17 and withdrawn claims 9-11 and 18-36 were canceled without prejudice to their pursuit in an appropriate continuation or divisional application. In the previously filed Amendment (October 29, 2007), new claim 53 was added.

Currently, claims 4-8, 12-14, 16, and 37-58 are pending in the application with claims 4, 12, 16, 46, and 47 being the independent claims. Claims 4, 7, 12, 16, 46, and 47 have been amended, and new claims 54-58 have been added.

III. The Interview with the Examiner

Applicants respectfully requested an interview with the Examiner. Applicants wish to express their gratitude for the Examiner's willingness to grant an interview on June 10, 2008. Applicants thank the Examiner accordingly.

IV. Acknowledgement of the Priority Claim is Requested

This application is a continuation application of U.S. Patent Application 09/736,659, filed 14 December 2000, which is a continuation-in-part of PCT application No. PCT/US00/10230, filed April 14, 2000, which claims the benefit of priority under 35 USC Section 119(e) of U.S. Provisional Patent Application No. 60/129,191, filed on April 14,

1999; U.S. Provisional Patent Application No. 60/180,353, filed on February 4, 2000; and U.S. Provisional Patent Application No. 60/193,556, filed on March 31, 2000, all of which are incorporated herein by reference.

Applicants respectfully request acknowledgement of the priority claim accordingly.

V. Withdrawal of Previous Rejections and Acknowledgement of the Declaration

Applicants thank the Examiner for withdrawing the rejection under 35 U.S.C. §102(b) for alleged anticipation by Bloch, the rejection under 35 U.S.C. §102(b) for alleged anticipation by Burgoyne, the rejection under 35 U.,S.C. §103(a) for alleged obviousness over Burgoyne in view of Ahern, and the rejection under 35 U.S.C. §103(a) for alleged obviousness over Burgoyne in view of Ahern and further in view of Bloch and Anderson.

Applicants also thank the Examiner for considering the Declaration of Dr. Walter King (mailed October 29, 2007).

VI. The Rejection of Claims 4-8, 12-17, and 37-53 under 35 U.S.C. §103(a) over Burgoyne in view of Bloch is Traversed, but Accommodated in Part and Moot in Part

The Examiner has rejected claims 4-8, 12-17, and 37-53 under 35 U.S.C. 103(a) as unpatentable over Burgoyne (U.S. Patent 5,496,562) in view of Bloch (U.S. Patent 4,789,630). Applicants traverse this rejection, but have accommodated it in part.

Applicants respectfully submit that claim 15 was previously canceled, and the rejection is moot with respect to this claim.

The rejection is discussed at length in the Office Action. The Patent Office alleges, in pertinent part:

> Burgoyne does not teach wherein the dry substrate or blood card is packaged in the form of a kit or wherein the external substance of the indicator generates a signal in an assay. [Par. 6, p. 4.]

The Patent Office also alleges, in pertinent part:

> Since Bloch et al. recognizes a need for immunodiagnostic kits that are capable of rapidly detecting a target molecule of interest, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention to improve the dry solid matrix of Burgoyne by including an indicator means, wherein the indicator is a color or fluorescent indicator, for the predictable result of enabling a rapid identification of a target biological molecule.
>
> Additionally, since the addition of an indicator to the dry solid matrix of Burgoyne would not effect the function of the dry solid matrix, and could be easily combined with the dry solid matrix as taught by Bloch et al., it would be obvious to one having ordinary skill in the art to utilize an indicator capable of generating a signal in an assay for the predictable results of detecting a target molecule of interest in a rapid, simple and efficient manner without the need for numerous reagents and materials. Such material in a kit would provide added convenience to the practitioner. [Par. 6, p. 5.]

Applicants respectfully disagree. Applicants have discussed both Burgoyne and Bloch at length in the record and refer the Examiner to this discussion.

As the Patent Office concedes, the ink-stamp or pencil marking of Burgoyne is not an "indicator comprising an external substance which generates a signal in an assay."

Applicants further submit that an ink-stamp or pencil marking, which would be used manually to record information in the manner of marginal notations, does not necessarily

suggest the use of an "indicator comprising an external substance which generates a signal in an assay."

In addition, as Dr. Walter King, Vice President of Research & Development of Whatman PLC, stated in his Declaration (submitted with the previous Amendment on October 29, 2007), Burgoyne discloses a "strong anionic detergent that binds to and denatures proteins" (col. 4, ll. 7-8), one that "will denature proteins and the majority of any pathogenic organisms in the sample" (col. 3; ll. 10-11). One of ordinary skill in the art would have expected the enzyme of the assay of the present invention to be denatured or otherwise inactivated upon contact with the "cellular lysis reagent comprising an anionic surfactant or detergent at a concentration which induces cellular lysis."

Applicants respectfully submit that Bloch does not remedy the deficiencies of Burgoyne and that the references teach away from the other.

As noted previously, Bloch is directed to Southern blotting, dot blotting, and similar techniques and applies purified DNA in an anionic detergent solution to a solid membrane surface for the detection of specific areas of the DNA or, alternatively, the use of such detergents to wash the solid phase after incubation for blocking purposes in order to reduce background with respect to analytical sensitivity (e.g., col. 20; lines 22-39).

For instance, Example 5 of Bloch (e.g., col. 33, lines 54-67) involves human **DNA, which has already been isolated, restriction digested, and electrophoresed before being transferred to a blot**. During the pre-hybridzation and hybridization steps, **when the Bloch blot is exposed to the SDS, it is wet, unlike the SDS-containing dry solid medium of the present invention or the SDS-containing dry solid medium of Burgoyne**. The pre-hybridization and hybridization solutions of Example 5 are only 0.5% SDS. Detection takes place after rinsing the blot with Buffer A, which contains 5% Triton X-100 (e.g., col. 35,

lines 39-44). The final concentration of Triton X-100 is not provided, but the addition of 5% Triton X-100 to another solution would result in a final concentration of less than 5%.

As noted in the Declaration of Dr. Walter King (previously submitted October 29, 2007), the cellular lysis reagent of **the present invention comprises an anionic detergent or surfactant**. In contrast, Triton X-100 is a non-ionic detergent. Thus, Bloch makes no distinction between ionic and non-ionic detergents. (For further discussion of this point, the Examiner's attention is directed to the remarks in the Amendment submitted October 29, 2007 and the accompanying Declaration of Dr. Walter King.)

In Example 6 of Bloch (e.g., col. 36, lines 40-47), cell lysis takes place in a tissue culture dish to which a lysis buffer (0.20 M LiCl, 0.020 M Tris CL, 0.001 M EDTA, 0.5% Nonidet P-40 and 0.05% aprotinin, pH 80) has been added directly, followed by addition of an equal volume of 5% SDS, 1M dithiotreitol, 10% glycerol, 0.005% bromphenol blue, 0.125 M Tris Cl, pH 6.8 (col. 36, lines 40-47). Addition of an equal volume of a solution comprising 5% SDS to a solution comprising 0.5% Nonidet P-40 results in a solution of **only** 2.5% SDS and 0.25% Nonidet P-40, and **the lysis takes place in solution** in a culture dish – **not on a dry solid medium**, as in the present invention. Again, as noted in Dr. King's Declaration, the cellular lysis reagent of the present invention comprises an anionic detergent or surfactant. In contrast, Nonidet P-40 is a non-ionic detergent. Thus, Bloch makes no distinction between ionic and non-ionic detergents.

In contrast, current claims 4, 12, 16, 46, and 47 and the claims dependent thereon, are directed to a **dry** substrate, the **dry** substrate comprising a solid matrix **and** a coating **sorbed to** the solid matrix. With respect to the present claims, the "**cellular lysis reagent** comprising an anionic surfactant or detergent" is present "**at a concentration which induces cellular lysis**."

Moreover, **at the concentrations which induce lysis**, the **enzymatic detection methods of Bloch** would be expected to be **inoperable** due to the denaturation of the enzyme. The cells, blood, or other biological sample are brought into contact with the dry substrate, which itself facilitates cellular lysis. The nucleic acid is maintained on the solid matrix, where it is detected.

The other discussions of anions in Bloch relate either to blocking solutions for the inhibition of non-specific binding on the wet membrane or to precipitation of the dye ion. These points have been discussed at length in the Amendment and Declaration submitted on October 29, 2007, and Applicants respectfully direct the Examiner's attention to these discussions regarding the unsuitability of these methods for the present invention.

With respect to the former instance (i.e., the blocking solutions), in Example 9 (e.g., col. 41, lines 57-65), the DNA is isolated, restriction digested, and electrophoresed prior to being blotted. In this Example, Bloch uses 0.5% SDS in a prehybridization mixture (5X Denhardt's solution with 50% formamide, 5X SSPE, 0.5% SDS, 5% dextran sulfate and 50% formamide) (col. 41, lines 57-60) and the same mixture containing two probes as a hybridization solution (col. 41, lines 62-65).

With respect to the latter instance, the anionic surfactants of Bloch are directed toward facilitating use of the dye ion (i.e., controllable precipitation of the meriquinone), rather than lysing the cells, and to the detection of DNA, for example, as part of a dot blot of previously isolated DNA or a blot of cells which are subsequently lysed by wetting with a separate lysis buffer, or after the DNA has been run on a gel (see, e.g., Bloch at col. 4, ll. 59-66; col. 10, ll. 47-61; and col. 11, ll. 20-27).

In addition to noting the range of "polymeric anions", Bloch states:

> ....Increased anion concentration and lowered reaction temperature favor salt precipitation or complex ion formation, with **anion concentrations of 10^{-3} to 10^{-1} M** and reaction temperatures of 0 to 60 C being preferred. [Col. 17; ll. 12-16; emphasis added.]

According to the Sigma catalog, Biochemicals, Reagents & Kits for Life Science Research, p. 2188 (Sigma-Aldrich Co., 2006-2007) (copy previously provided), SDS has a molecular weight (FW) of 288.38. The present specification teaches that **one example of a lysis reagent** that can be used in accordance with the present invention **is 5% - 10% SDS** and notes that increased concentrations of SDS can provide "greater critical micelle concentration which generates greater lysing capability and thus greater yield of target nucleic acid" (p. 11.). As noted previously, 5% - 10% SDS would be the equivalent of 0.17 M – 0.35 M, which would be greater than the 10^{-3}M – 10^{-1}M range of Bloch. Therefore, the disclosure of Bloch teaches away from the present invention.

In the present invention, the chemical coating is already sorbed to the matrix to result in a **dry** solid medium comprising the chemical coating, while Bloch describes the application of purified DNA in an anionic detergent **solution** to a solid membrane surface for the detection of specific areas of the DNA, or, alternatively, the use of such detergents to **wash** the solid phase after incubation for blocking purposes in order to reduce background with respect to analytical sensitivity (col. 20; lines 22-39) or for the precipitation of the dye ion (col. 4, ll. 59-66; col. 10, ll. 47-61; col. 11, ll. 20-27; and col. 17, ll. 12-16).

Bloch reinforces the criticality of this point by the emphasis on the use of an integrity device that is intended to keep the membrane wet and prevent it from drying out (col. 35, line 68, to col. 36, line 1). In contrast, the integrity maintenance means (e.g., a plastic bag) of the present invention has the exact opposite purpose – namely, to keep the membrane dry to stop bacterial or fungal growth while simultaneously preventing loss in the event that the dry membrane becomes too brittle.

With respect to the integrity maintenance means of the present invention (e.g., claims 7, 12, 16, and 46, Applicants respectfully refer the Examiner to the specification:

> The term "integrity maintainer" or "integrity maintenance means" as used herein means a scalable member that prevents degradation and/or loss of the matrix. Preferably, the integrity maintainer of the present invention creates an air tight seal thus, preventing air, bacteria or other contaminants from coming into contact with the matrix and purified nucleic acid. The integrity maintainer can be in the form of a plastic bag, with or without a seal, cellophane, a sealable container, parafilm and the like.
>
> The integrity maintainer can open to allow application of a sample onto the matrix. It is then closed and sealed thereby containing the substrates. Accordingly, if the substrate ages and becomes brittle, it is contained and not lost. Alternatively, the integrity maintainer can be applied over the substrate after the sample is applied. [P. 13, l. 28-p. 14, l. 9.]

The present invention comprises a **dry** solid medium. Unlike Bloch, where the "wetness" of the membrane is maintained, the integrity maintainance means of the present invention maintains the condition of the dry solid medium while preventing loss should it become too old or brittle, as well as limiting its exposure to bacteria and other contaminants.

As discussed above, the present invention is directed to a kit comprising a cellular lysis reagent comprising an anionic detergent or surfactant. The present specification teaches that **one example of a lysis reagent** that can be used in accordance with the present invention **is 5% - 10% SDS** and notes that increased concentrations of SDS can provide "greater critical micelle concentration which generates greater lysing capability and thus greater yield of target nucleic acid" (p. 11.). As discussed previously by Dr. King in his Declaration, **at these concentrations, the enzymatic detection methods of Bloch would be expected to be inoperable due to inactivation of the detection enzymes.**

Nor would one of ordinary skill in the art be motivated to combine Burgoyne and Bloch to arrive at the present invention. The present invention is **not a combination,**

simple substitution, or improvement of known elements or methods to yield a predictable result. One of ordinary skill in the art would **not have considered it "obvious to try" with any reasonable expectation of success.**

Burgoyne discloses a "strong anionic detergent that binds to and denatures proteins" (col. 4, ll. 7-8), one that "will denature proteins and the majority of any pathogenic organisms in the sample" (col. 3; ll. 10-11). One of ordinary skill in the art would have expected the enzyme of the assay of the present invention to be denatured or otherwise inactivated upon contact with the "cellular lysis reagent comprising an anionic surfactant or detergent at a concentration which induces cellular lysis."

Likewise, **at the concentrations which induce lysis**, the **enzymatic detection methods of Bloch** would be expected to be **inoperable** due to the denaturation of the enzyme. Therefore, one of ordinary skill in the art would have expected the enzymes of Bloch to be denatured when exposed to the dry solid medium of Burgoyne, leaving the enzymatic detection methods of Bloch inoperable.

Moreover, **one of ordinary skill** in the art **would have expected the enzymes of Bloch to be denatured** when exposed to **the dry solid medium of the present invention, leaving the enzymatic detection methods of Bloch inoperable**:

> ...The denaturing reagent can be **a surfactant** that will ***denature proteins*** and the majority of any pathogenic organisms in the sample. **Anionic detergents are examples of such denaturing reagents**....[P. 10, lines 25-28; emphasis added.]

Thus, **the unpredictability of the present invention goes far beyond** a combination, simple substitution, or improvement of known elements or methods and would **not** have been "obvious to try."

Applicants respectfully submit that remaining claims 4-8, 12-14, 16-17, and 37-53 fulfill the requirements of 35 U.S.C. §103(a), thereby placing these claims in condition for allowance, and request the Examiner's reconsideration accordingly.

CONCLUSION

In view of the foregoing amendments and remarks, the present application is respectfully considered in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited.

It is believed that all outstanding rejections have been addressed by this submission and that all the claims are in condition for allowance. If discussion of any amendment or remark made herein would advance this important case to allowance, the Examiner is invited to call the undersigned as soon as convenient.

Applicants hereby request a three-month extension of time. If, however, a request for an additional extension of time is required, the Examiner is respectfully requested to treat this as a conditional request for an additional extension of time. Although it is not believed that any additional fee (in addition to the fee concurrently submitted) is required to consider this submission, the Commissioner is hereby authorized to charge our deposit account no. 04-1105 should any fee be deemed necessary.

Respectfully submitted,

Date: June 27, 2008

Kathryn A. Piffat, Ph.D. (Reg. No. 34,901)
Intellectual Property Practice Group
Edwards Angell Palmer & Dodge, LLP
P.O. Box 55874
Boston, Massachusetts 02205
Telephone: 617-517-5516
Attorney/Agent for the Applicant(s)

Customer No. 21874